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(54) Depottablette

(57) Depottablette, die als Depotbasisbestandteil Hydroxypropylmethylcelluloseteilchen enthält, deren Schüttdichte nicht mehr als 0,35 g/ml beträgt, wobei nicht weniger als 95 Massen% ein (100 mesh-)Sieb mit 0,15 mm Maschenweite passieren können und die einen Substitutionsgrad an Methoxygruppen von 19 bis 30 Massen% und einen Substitutionsgrad an Hydroxypropoxygruppen von 4 bis 12 Massen% haben.

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Beschreibung

Die vorliegende Erfindung betrifft eine Depottablette vom Matrixtyp, die einen pharmazeutisch wirksamen Bestandteil in festgelegten Raten freisetzen kann.

Die Verträglichkeit zwischen einem Patienten und einer Arznei sollte verbessert werden, falls die Arznei beispielsweise einen Nebeneffekt hat. Eine Depottablette ist ein Medikament, bei dem die Abgaberate an einen bestimmten pharmazeutisch wirksamen Bestandteil an den Körper so kontrolliert werden kann, daß der medizinische Bestandteil kontinuierlich mit einer festgelegten niedrigen Konzentration freigesetzt wird, wobei der Blutpegel an diesem bestimmten medizinischen Bestandteil so kontrolliert werden kann, daß er nicht höher als ein festgelegter Pegel wird, so daß dessen Verträglichkeit für einen Patienten verbessert wird. Zusätzlich erlaubt die Depottablette eine Verringerung der Häufigkeit der Arzneiverabreichung. Aus diesem Grund muß die Depottablette ihre Wirksamkeit über einen langen Zeitraum beibehalten können.

Verschiedene Arten von Depottabletten sind bekannt, z. B. eine vom Matrixtyp, die durch Vermischen eines pharmazeutisch wirksamen Bestandteils, eines wasserlöslichen Polymers und eines Wachses und anschließendem Pressen des resultierenden Gemisches gebildet wird; eine vom Kapseltyp, die enterische Körnchen, die einen pharmazeutisch wirksamen Bestandteil enthalten, und einen medizinischen Bestandteil enthält, die in eine Kapsel eingebracht worden sind; und eine vom Mehrfachtyp, die durch Verpressen eines pulvrigen Bestandteils erhalten wird, der einen pharmazeutisch wirksamen Bestandteil enthält.

Die Depottablette vom Matrixtyp wird auch als eine vom Diffusionsgeschwindigkeit-bestimmenden Typ bezeichnet. Der darin enthaltene pharmazeutisch wirksame Bestandteil wird aufgrund des Konzentrationsgradienten an dem Bestandteil selbst nach außen (d. h. das Äußere der Tablette) abgegeben, der aufgrund des Eindringens von Wasser aufgebaut wird, das als die treibende Kraft für dieses Abgabephänomen wirkt. Die Diffusionsgeschwindigkeit des pharmazeutisch wirksamen Bestandteils wird durch die geeignete Wahl eines Depotbasisbestandteils kontrolliert. Unter den Matrixtypen wird für Depottabletten vom Gelmatrixtyp Hydroxypropylmethylcellulose (HPMC) als Depotbasisbestandteil verwendet, die eine wasserlösliche polymere Verbindung ist. Wenn eine solche Depottablette einem Patienten verabreicht wird, bildet HPMC oder ähnliches in dem Körper des Patienten eine Gelschicht auf deren Oberfläche, so daß die Abgabegeschwindigkeit an deren pharmazeutisch wirksamen Bestandteil kontrolliert wird. Die meisten charakteristischen Eigenschaften der Depotpräparate werden hauptsächlich durch die Eigenschaften des bestimmten ausgewählten Depotbasisbestandteils bestimmt, und besonders wichtige Faktoren sind insbesondere das Molekulargewicht und die Hydratisierungsgeschwindigkeit (Lösungsgeschwindigkeit) der ausgewählten Depotbasis.

Im Fall, daß die Depottablette einen sehr wasserlöslichen medizinischen Bestandteil enthält oder die Depottablette einen großen Gehalt an medizinischem Bestandteil enthält, ist es erforderlich, daß der Depotbasisbestandteil insbesondere die Lösung des pharmazeutisch wirksamen Bestandteils gut verzögert, d. h. daß er die Auflösungsgeschwindigkeit des pharmazeutisch wirksamen Bestandteils in dem Körper kontrollieren kann.

Depottabletten vom Matrixtyp sind verglichen mit denjenigen vom Mehrfachtyp leicht herstellbar und billig. Die in der japanischen Patentanmeldung mit der Veröffentlichungsnummer 58-110531 beschriebene Depottablette enthält HPMC, deren 2% wäßrige Lösung eine Viskosität von nicht mehr als 800 cP, gemessen bei 20°C, hat, und die einen Substitutionsgrad an Hydroxypropoxygruppen von 9 bis 12 Massen% hat. Andererseits enthält die in der japanischen Patentanmeldung mit der Veröffentlichungsnummer 4-15208 beschriebene Depottablette als Depotbasisbestandteil wenigstens 25,8 Massen% HPMC, deren 2% wäßrige Lösung eine Viskosität von nicht mehr als 800 cP, gemessen bei 20°C, hat. In diesem Fall hat die verwendete HPMC einen Substitutionsgrad an Hydroxypropoxygruppen von 4 bis 32 Massen% und einen Substitutionsgrad an Methoxygruppen von 16 bis 24 Massen%.

Bei diesen herkömmlichen Depottabletten beginnen die Depotbasisbestandteile durch Hydratisierung oder Auflösung in Wasser zu schwellen und bilden dann Gelschichten, wenn sich deren pharmazeutisch wirksame Bestandteile aufzulösen beginnen. Wenn die Teilchengröße des Depotbasisbestandteils groß ist, ist deren Hydratisierungsgeschwindigkeit gering und das Ausmaß des Anschwellens, das während der Hydratisierung beobachtet wird, ist hoch. Dies verursacht Probleme solcher Art, daß sich die Tablette auflöst, bevor der Depotbasisbestandteil eine ausreichende Gelschicht ausbildet und im Ergebnis wird die Abgabegeschwindigkeit des wirksamen Bestandteils nicht wirksam kontrolliert. Zudem ergibt ein Basisbestandteil mit solch großer Teilchengröße keine Tablette mit erwünschter Härte, die resultierende Tablette wird im Anfangsstadium der Abgabe zersetzt und dementsprechend hat die Tablette oft keine ausreichenden Depotcharakteristiken.

Die japanische Patentanmeldung mit der Veröffentlichungsnummer 62-149632 beschreibt eine Depottablette, die ebenfalls HPMC als Matrixbasisbestandteil verwendet. In diesem Fall hat die 2% wäßrige Lösung der verwendeten HPMC eine Viskosität von wenigstens 800 cP, gemessen bei 20°C, einen Substitutionsgrad an Hydroxypropoxygruppen von 7 bis 12 Massen% und einen Substitutionsgrad an Methoxygruppen von 28 bis 30 Massen%. Zudem ist deren Teilchengröße so eingestellt, daß nicht weniger als 95 Massen% der Teilchen ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren.

Es ist Aufgabe der vorliegenden Erfindung, eine Depottablette zur Verfügung zu stellen, in der die Abgabegeschwindigkeit an deren pharmazeutisch wirksamen Bestandteil wirksam und kontinuierlich kontrolliert werden kann.

Die erfindungsgemäße Depottablette enthält als einen Depotbasisbestandteil Hydroxypropylmethylcelluloseteilchen, die einen Substitutionsgrad an Methoxygruppen von 19 bis 30 Massen%, einen Substitutionsgrad an Hydroxypropoxygruppen von 4 bis 12 Massen% haben, wovon nicht weniger als 95 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren können und deren Schüttdichte nicht mehr als 0,35 g/ml ist.

Die Viskosität einer 2% wäßrigen Lösung der Hydroxypropylmethylcelluloseteilchen beträgt nicht weniger als 1000 cP, gemessen bei 20°C, und der Gehalt an Hydroxypropylmethylcellulose in der Tablette beträgt 5 bis 90

Massen%.

Die Erfinder dieser Erfindung haben festgestellt, daß, wenn eine Depottablette zur Kontrolle der Abgabegeschwindigkeit eines pharmazeutisch wirksamen Bestandteils verwendet wird, die Abgabegeschwindigkeit an dem pharmazeutisch wirksamen Bestandteil maßgeblich durch die Teilchengröße des Depotbasisbestandteils, d. h. HPMC, die Substitutionsgrade an Methoxygruppen und Hydroxypropoxygruppen und die Viskosität von deren wäßriger Lösung sowie die sogenannte Schüttdichte beeinflußt wird. Die Schüttdichte ist das gewogene lose beladene Material pro Einheit.

Die erfindungsgemäße Depottablette, die anhand der vorstehenden Feststellungen entwickelt worden ist, enthält als einen Depotbasisbestandteil HPMC-Teilchen, die einen Substitutionsgrad an Methoxygruppen von 19 bis 30 Massen%, einen Substitutionsgrad an Hydroxypropoxygruppen von 4 bis 12 Massen% haben. Deren Teilchengröße liegt in einem Bereich von nicht weniger als 0,15 mm Maschenweite (100 mesh). Genauer können nicht weniger als 95 Massen% der Teilchen ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren. Die Schüttdicht der HPMC-Teilchen beträgt nicht mehr als 0,35 g/ml. Die Schüttdichte der HPMC-Teilchen wird bestimmt, indem das Gewicht der Teilchen gemessen wird, die erforderlich sind, um ein festgesetztes Volumen ohne Anwendung von Kraft auszufüllen, wobei ein Apparat zum synthetischen Bestimmen von Eigenschaften von pulvrigen Substanzen verwendet wird. Die hier eingesetzte HPMC hat einen Substitutionsgrad an Methoxygruppen von 19 bis 30 Massen%, einen Substitutionsgrad an Hydroxypropopxygruppen von 4 bis 12 Massen%.

Die Viskosität einer 2% wäßrigen Lösung der HPMC ist vorzugsweise nicht niedriger als 1000 cP, gemessen bei 20°C. Mit Zunahme des Molekulargewichts nimmt die elastische Festigkeit des Gels zu, das durch Hydratisierung des HPMC-Bestandteils gebildet wird, und bewirkt entsprechend die Verringerung der Abgabegeschwindigkeit eines pharmazeutisch wirksamen Bestandteils. Der Gehalt der vorstehenden HPMC in der erfindungsgemäßen Depottablette beträgt vorzugsweise 5 bis 90 Massen% und noch bevorzugter 10 bis 50 Massen%. Der Grund hierfür ist, daß die resultierende Tablette kein ausreichendes Depotvermögen aufweist, wenn er weniger als 5 Massen% ist, wohingegen die Abgabegeschwindigkeit an wirksamem Bestandteil in der Endstufe, in der der Restgehalt an wirksamem Bestandteil aufgrund dessen kontinuierlicher Abgabe verringert ist, abnimmt, wenn er 90 Massen% übersteigt.

Die hier verwendete HPMC kann hergestellt werden, indem eine Masse mit einem erwünschten Verätherungsmittel in Gegenwart eines Alkali-Katalysators, wie Natriumhydroxid, umgesetzt wird. Die vorstehende HPMC, die erfindungsgemäß als Depotbasisbestandteil verwendet wird, ist z. B. HPMC 2906, HPMC 2208 und HPMC 2910, die in The Pharmacopoeia of Japan (Abschnitt 12) beschrieben sind. HPMC von diesem Typ sind kommerziell beispielsweise von Shin-Etsu Chemical Co., Ltd. unter den Handelsnamen Methollose 60SH-4000, Methollose 60SH-10000, Methollose 90SH-4000, Methollose 90SH-15000, Methollose 90SH-30000 und Methollose 90SH-100000 erhältlich. Diese HPMC-Produkte haben Viskositäten (2% wäßrige Lösung, 20°C) von 4000 cP, 10 000 cP, 4000 cP, 15 000 cP, 30 000 cP bzw. 100 000 cP.

Im allgemeinen enthält die Depottablette wenigstens einen pharmazeutisch wirksamen Bestandteil (Arzneimittel) und andere für Arzneimittel erforderliche Additive. Beispiele für pharmazeutisch wirksame Bestandteile umfassen Theophyllin, Aspirin, Acetoaminophen, Ethenzamid, Ibuprofen, Naproxen, Propranolol, Methyldopa, Furosemid, Nifedipin, Pindolol, Captopril, Erythromycin, Procainamid, Chiningluconat, Chininsulfat, Isosorbiddinitrat, Vitaminpräparate wie Vitamin C, B_1, B_2, B_6 und Folsäure, Eisenpräparate wie Eisen(II)sulfat und Kalziumchlorid. Diese wirksamen Bestandteile können, auch wenn ein hydrophiler wirksamer Bestandteil oder ein effektiver Bestandteil in hoher Konzentration verwendet werden muß, effizient in den Basisbestandteil eingebracht werden. Die Menge an medizinischem Bestandteil, die der Tablette zugesetzt werden soll, variiert in Abhängigkeit der charakteristischen Eigenschaften jedes besonderen wirksamen Bestandteils, der ausgewählt wird, und beträgt 10 bis 95 Massen%.

Additive für Arzneimittel, die der Tablette gegebenenfalls zusätzlich zu den vorstehenden pharmazeutisch wirksamen Bestandteilen zugesetzt werden, umfassen beispielsweise Vehikel, preßerleichternde Zusätze, Stabilisatoren und oberflächenaktive Mittel. Bestimmte Beispiele für Vehikel sind Maisstärke, Lactose, Sucrose und Mannose. Ein preßerleichternder Zusatz kann beispielsweise Magnesiumstearat sein. Diese preßerleichternden Zusätze können der Tablette in einer Menge von 0,5 bis 3,0 Massen% zugesetzt werden.

Im Fall einer Depottablette vom nassen Matrixtyp, die durch das Naßverfahren gebildet wird, werden ihr Bindemittel als andere Additive für Arzneimittel zugesetzt. In diesem Fall wirkt der vorstehende HPMC-Bestandteil, der der Depotbasisbestandteil ist, auch als Bindemittel, die Tablette kann jedoch ebensogut andere Arten von HPMC, Hydroxypropylcellulose und/oder Polyvinylpyrrolidon enthalten. Im allgemeinen wird solch ein Bindemittel in einer Menge von 2 bis 5 Massen%, bezogen auf das Gesamtgewicht der Tablette, eingesetzt.

Die erfindungsgemäße Depottablette kann mit einem Trocken- oder Naßverfahren hergestellt werden. Bei dem Trockenverfahren wird die Depottablette durch einheitliches Vermischen eines pulvrigen pharmazeutisch wirksamen Bestandteils, eines HPMC-Produkts als ein Depotbasisbestandteil und eines Vehikels unter trockenen Bedingungen erhalten, wobei zudem ein preßerleichterndes Mittel zugesetzt wird und das resultierende Gemisch beispielsweise mit einer routierenden Preßmaschine verpreßt wird. Als HPMC-Produkt wird die vorstehende HPMC verwendet, die eine ausreichend feine Teilchengröße und eine niedrige Schüttdichte hat. Bei dem Naßverfahren kann andererseits die Depottablette durch Vermischen eines pulvrigen pharmazeutisch wirksamen Bestandteils, eines HPMC-Produkts mit ausreichend feiner Teilchengröße und eines Vehikels in Gegenwart von Wasser, eines organischen Lösungsmittels oder eines Gemisches daraus in einem Hochgeschwindigkeitsrührapparat, Trocknen des resultierenden Gemisches und Durchleiten des getrockneten Produkts durch ein Sieb, um Körnchen zu erhalten, erhalten werden. Die resultierenden Körnchen werden mit anderen Zusätzen, wie einem preßerleichternden Zusatz, vermischt und in einer routierenden Preßmaschine formgepreßt.

Wenn eine Depottablette von diesem Typ einem Patienten verabreicht wird, schwillt der darin enthaltene

HPMC-Bestandteil durch schnelle Hydratisierung in dem Körper des Patienten an und bildet so auf der Oberfläche der Tablette eine Gelschicht. Die Abgabegeschwindigkeit des pharmazeutisch wirksamen Bestandteils wird durch verschiedene Faktoren, wie das Molekulargewicht der HPMC, die die Gelschicht bildet, und deren Hydratisierungsgeschwindigkeit, stark beeinflußt.

Wenn HPMC-Teilchen mit einer Größe von nicht weniger als 0,15 mm Maschenweite (100 mesh) formgepreßt werden, bewirken die Teilchen eine dichte Agglomeration und dies wiederum verhindert die vorzeitige Zersetzung der Tablette in dem Anfangsstadium der Abgabe und jede Abgabe des darin enthaltenen Arzneimittels im Überschuß. Andererseits bewirken HPMC-Teilchen mit großer Teilchengröße beim Formpressen Agglomeration, jedoch haben die resultierenden Agglomerate eine grobe Dichte. Die Schüttdichte beeinflußt das Formpreßvermögen solcher Teilchen, die grob agglomerieren, stark. Wenn die Schüttdichte weniger als 0,35 g/ml ist, bewirken die HPMC-Teilchen, die eine Teilchengröße von nicht weniger als 0,15 mm Maschenweite (100 mesh) haben, eine Zunahme der Härte nach dem Formpressen und eine Zunahme der Hydratisierungsgeschwindigkeit. Andererseits, wenn die Schüttdichte niedrig ist, nimmt die Oberfläche der HPMC-Teilchen zu und dies bewirkt eine Verbesserung des Formpreßvermögens der Teilchen.

Die erfindungsgemäße Depottablette mit der vorstehenden Struktur erlaubt eine leichte Kontrolle der Abgabegeschwindigkeit eines medizinischen Bestandteils bis zu einem vorbestimmten niedrigen Niveau und ermöglicht die kontinuierliche Abgabe des medizinischen Bestandteils in vorbestimmter Konzentration über einen langen Zeitraum.

Die vorliegende Erfindung wird im folgenden unter Bezugnahme auf die folgenden Beispiele genauer erläutert, jedoch ist die vorliegende Erfindung keinesfalls auf diese spezifischen Beispiele beschränkt.

Beispiel 1

Nachdem 200 mg Salicylamid und 50 mg HPMC einheitlich vermischt worden waren, wurde das resultierende Gemisch bei einem Druck von 100 kg/cm^2 30 Sekunden in einer IR-Preßmaschine verpreßt, wobei eine Depottablette erhalten wurde. Die hier verwendete HPMC war HPMC 2910 (erhältlich von Shin-Etsu Chemical Co., Ltd. unter dem Handelsnamen Methollose 60SH-4000), wovon nicht weniger als 95 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten und die eine Schüttdichte von 0,25 g/ml hatte.

Beispiel 2

Dasselbe Verfahren wie in Beispiel 1 wurde mit der Ausnahme wiederholt, daß die Schüttdichte der verwendeten HPMC auf 0,30 g/ml eingestellt war.

Vergleichsbeispiele 1 und 2

Dasselbe Verfahren wie in Beispiel 1 wurde mit der Ausnahme wiederholt, daß die Schüttdichte der verwendeten HPMC auf 0,45 g/ml oder 0,55 g/ml eingestellt war.

Beispiel 3

Nach gleichförmigem Vermischen von 240 mg Theophyllin, 60 mg HPMC und 3 mg Magnesiumstearat in einem Zwillingstrommelmischer wurde das resultierende Gemisch auf die übliche Weise verpreßt, wobei eine Depottablette erhalten wurde. Die hier verwendete HPMC war wie in Beispiel 1 HPMC 2910, von der nicht weniger als 98 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten und die eine Schüttdichte von 0,32 g/ml hatte.

Vergleichsbeispiel 3

Dasselbe Verfahren wie in Beispiel 3 wurde mit der Ausnahme wiederholt, daß eine HPMC verwendet wurde, von der nicht weniger als 80 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten und die eine Schüttdichte von 0,33 g/ml hatte.

Beispiel 4

Nach gleichförmigem Vermischen von 220 mg Ethenzamid, 80 mg HPMC und 3 mg Magnesiumstearat in einem Zwillingstrommelmischer wurde das resultierende Gemisch in der üblichen Weise verpreßt, wobei eine Depottablette erhalten wurde. Die hier verwendete HPMC war HPMC 2208 (erhältlich von Shin-Etsu Co., Ltd. unter dem Handelsnamen Methollose 90SH-100000), wovon nicht weniger als 95 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten und die eine Schüttdichte von 0,23 g/ml hatte.

Qualitätsuntersuchung

Jede der Depottabletten, die in den Beispielen 1 bis 4 und den Vergleichsbeispielen 1 bis 3 hergestellt worden war, wurde in einer Testlösung gemäß dem Rührverfahren, das in The Pharmacopoeia of Japan (Abschnitt 12) beschrieben ist, gelöst; die Abgabegeschwindigkeit wurde in Zeitintervallen bestimmt, und die Lösungsgeschwindigkeit wurde dann anhand der so bestimmten Abgabegeschwindigkeit ausgewertet. Die hier verwendete Testlösung war 900 ml Wasser, das bei 37°C gehalten wurde. Die Anzahl der Umdrehungen der Rührschaufel

wurde auf 100 U/min festgesetzt.

Die so erhaltenen Ergebnisse sind in der folgenden Tabelle 1 zusammengefaßt. In der Tabelle 1 ist die "verstrichene Zeit" in Stunden und die "Abgabegeschwindigkeit" in "Massen%" ausgedrückt.

Tabelle 1

Zeit	Lösungsgeschwindigkeit						
	Beispiele				Vergleichsbeispiele		
verstrichen	1	2	3	4	1	2	3
0,5	13,2	17,4	6,2	2,5	21,5	26,2	49,6
1,0	17,1	21,9	11,3	4,1	26,6	32,4	56,7
2,0	23,2	27,9	19,7	7,6	32,6	39,7	65,8
4,0	34,3	44,7	32,6	14,1	44,5	55,1	80,3
6,0	44,0	49,6	48,7	19,8	55,1	64,1	91,1
8,0	54,9	59,0	60,9	25,1	63,0	71,5	98,8
12,0	71,9	75,0	80,0	35,6	78,0	88,2	--

Die in den Beispielen 1 und 2 und in Vergleichsbeispielen 1 und 2 erhaltenen Ergebnisse zeigen deutlich, daß sich die Tablette in dem Anfangsstadium der Abgabe zu zersetzen beginnt, wobei der pharmazeutisch wirksame Bestandteil spontan mit hoher Geschwindigkeit abgegeben wurde, und die Tablette nicht die erwünschten andauernden Abgabecharakteristiken zeigte, wenn die Schüttdichte der verwendeten HPMC 0,35 g/ml überschritt. Die in Beispiel 3 und in Vergleichsbeispiel 3 erhaltenen Ergebnisse zeigen, daß die beobachtete Abgabegeschwindigkeit einer Abgabe nullter Ordnung entsprach, wenn HPMC-Teilchen verwendet wurden, von denen nicht weniger als 95 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten. Andererseits wurde festgestellt, daß sich die Tablette im Anfangsstadium der Abgabe zu zersetzen beginnt und daß der wirksame Bestandteil spontan mit hoher Geschwindigkeit abgegeben wird, wenn HPMC-Teilchen verwendet wurden, von denen weniger als 95 Massen% ein (100 mesh) Sieb mit 0,15 mm Maschenweite passieren konnten.

Patentansprüche

1. Depottablette, die als Depotbasisbestandteil Hydroxypropylmethylcelluloseteilchen enthält, deren Schüttdichte nicht mehr als 0,35 g/ml beträgt, wobei nicht weniger als 95 Massen% ein (100 mesh-)Sieb mit 0,15 mm Maschenweite passieren können und die einen Substitutionsgrad an Methoxygruppen von 19 bis 30 Massen% und einen Substitutionsgrad an Hydroxypropoxygruppen von 4 bis 12 Massen% haben.
2. Depottablette nach Anspruch 1, wobei die Viskosität einer 2% wäßrigen Lösung der Hydroxypropylmethylcellulose nicht weniger als 1000 cP, gemessen bei 20°C, beträgt.
3. Depottablette nach Anspruch 1 oder 2, wobei der Gehalt an Hydroxypropylmethylcellulose in der Tablette 5 bis 90 Massen% beträgt.

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DEPOT TABLET

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References cited: US 47 34 285

A depot tablet that contains as depot base component hydroxypropylmethylcellulose particles whose bulk weight is not more than 0.35 g/mL, where not less than 95 wt% can pass through a screen with 0.15 mm mesh size (100 mesh) and that have a degree of substitution of methoxy groups from 19 to 30 wt% and a degree of substitution of hydroxypropoxy group from 4 to 12 wt%.

Description

This invention concerns a depot tablet of matrix type that can release a pharmaceutically active component at fixed rates.

The tolerability for a patient and a drug should be improved if the drug has, for example, a side effect. A depot tablet is a medication in which the release rate of a specific pharmaceutically active component in the body can be controlled so that the medical component is released continuously at a fixed low concentration, and the blood level of this specific medical component can be controlled so that it does not become higher than a fixed level, so that its tolerability for a patient is improved. In addition, the depot tablet enables a reduction of the frequency of the drug administration. For this reason the depot tablet must be able to keep its efficacy over a long period of time.

Various types of depot tablets are known, for example a depot tablet of matrix type that is formed by mixing a pharmaceutically active component, a water-soluble polymer and a wax and then molding the resulting mixture under pressure; a depot tablet of capsule type, which contains enteric particles containing a pharmaceutically active component and a medical component, which are incorporated into a capsule; and a depot tablet of composite type which is obtained by molding a powdered component that contains a pharmaceutically active component under pressure.

The depot tablet of matrix type is also called a depot tablet of diffusion rate-determining type. The pharmaceutically active component contained in it is released to the outside (i.e., the outside of the tablet) because of the concentration gradient at the component itself, which is produced because of the penetration of water, which acts as the driving force for this release phenomenon. The diffusion rate of the pharmaceutically active component is controlled by the appropriate choice of depot base component. Among the matrix types hydroxypropylmethylcellulose (HPMC), which is a water-soluble polymer compound, is used as depot base component for depot tablets of gel matrix type. When such a depot tablet is administered to a patient, HPMC or a similar substance forms a gel layer on its surface in the patient's body, so that the release rate of its pharmaceutically active component is controlled. Most of the characteristic properties of the depot preparation are mainly determined through the

properties of the specific depot base component that is selected; particularly important factors are especially the molecular weight and hydration rate (dissolving rate) of the selected depot base.

If the depot tablet contains a very highly water soluble medical component or the depot tablet contains a high content of medical component, it is necessary that the depot base component do a good job of delaying in particular the dissolving of the pharmaceutically active component, i.e., that it can control the dissolving rate of the pharmaceutically active component in the body.

Compared to depot tablets of composite type, depot tablets of matrix type are easily produced and cheap. The depot tablet described in the Japanese Patent Application with the Publication No. 58-110531 contains HPMC, a 2% aqueous solution of which has a maximum viscosity of 800 cP measured at 20°C and which has a degree of substitution of hydroxypropoxy groups from 9 to 12 wt%. On the other hand, the depot tablet described in the Japanese Patent Application with the Publication No. 4-15208 as depot base component contains at least 25.8 wt% HPMC, a 2% aqueous solution of which has maximum viscosity of 800 cP measured at 20°C. In this case the HPMC that is used has a degree of substitution of hydroxypropoxy groups from 4 to 32 wt% and a degree of substitution of methoxy groups from 16 to 24 wt%.

With these traditional depot tablets the depot base components begin to swell in water through hydration or dissolving and then form gel layers when their pharmaceutically active components begin to dissolve. If the particle size of the depot base component is large, its hydration rate will be low and the extent of swelling that is seen during hydration will be high. This gives rise to problems such that the tablets dissolve before the depot base component forms a sufficient gel layer and, as a result, the release rate of the active component is not effectively controlled. In addition, a base component with such large particle sizes will not produce tablets with the desired hardness, the resulting tablets will decompose in the initial stage of release and accordingly the tablets frequently do not have sufficient depot characteristics.

The Japanese Patent Application with the Publication No. 62-149632 describes a depot tablet that likewise uses HPMC as matrix base component. In this case a 2% aqueous solution of the HPMC has a viscosity of at least 800 cP measured at 20°C, a degree of substitution of hydroxypropoxy groups from 7 to 12 wt% and a degree of substitution of methoxy groups from 28 to 30 wt%. In addition, its particle size is adjusted so that no less than 95 wt% of the particles passes through a screen with 0.15 mm mesh size (100 mesh).

A task of this invention is to make available a depot tablet in which the release rate of its pharmaceutically active component can be effectively and continuously controlled.

The depot tablet in accordance with the invention contains as a depot-based component hydroxypropylmethylcellulose particles that have a degree of substitution of methoxy groups from 19 to 30 wt%, a degree of substitution of hydroxypropoxy groups from 4 to 12 wt%, of

which no less than 95 wt% can pass through a screen with 0.15 mm mesh size (100 mesh) and whose bulk weight is no more than 0.35 g/mL.

The viscosity of a 2% aqueous solution of the hydroxypropylmethylcellulose particles is at least 1000 cP measured at 20°C and the content of hydroxypropylmethylcellulose in the tablet is 5 to 90 wt%.

The inventors of this invention established that if a depot tablet is used to control the release rate of a pharmaceutically active component, the release rate of the pharmaceutically active component is decisively affected by the particle size of the depot base component, i.e., the HPMC, the degrees of substitution of methoxy group and hydroxypropoxy groups, and the viscosity of an aqueous solution of it as well as said bulk weight. The bulk weight is the weighed loose material per unit [sic].

The depot tablet in accordance with the invention, which was developed on the basis of the above statements, contains as a depot base component HPMC particles that have a degree of substitution of methoxy groups from 19 to 30 wt%, a degree of substitution of hydroxypropoxy groups from 4 to 12 wt%. Their particle size lies in the range from not less than 0.15 mm mesh size (100 mesh). More precisely no less than 95 wt% of the particles can pass through a screen with 0.15 mm mesh size (100 mesh). The bulk weight of the HPMC particles is no more than 0.35 g/mL. The bulk weight of the HPMC particles is determined by measuring the weight of the particles that are necessary to fill a fixed volume without application of force, using an apparatus for synthetic determination of the properties of powdered substances. The HPMC that is used here has a degree of substitution of methoxy groups from 19 to 30 wt% and a degree of substitution of hydroxypropoxy groups from 4 to 12 wt%.

The viscosity of a 2% aqueous solution of the HPMC is preferably no less than 1000 cP measured at 20°C. The elastic strength of the gel that is formed by hydration of the HPMC component increases with increasing molecular weight and correspondingly brings about a decrease of the release rate of a pharmaceutically-active component. The content of said HPMC in the depot tablet in accordance with the invention is preferably 5 to 90 wt% and more preferably 10 to 50 wt%. The reason for this is that the resulting tablet will not have sufficient depot capacity if it is less than 5 wt%, where in contrast the release rate of active component in the end stage, in which the residual content of active component has decreased because of its continuous release, will decrease if is exceeds 90 wt%.

The HPMC used here can be produced by reacting a substance with a desired etherification agent in the presence of an alkali catalyst. Said HPMC that is used in accordance with the invention as depot base material is, for example, HPMC 2906, HPMC 2208 or HPMC 2910, which are described in the Pharmacopoeia of Japan (Section 12). HPMCs of this type are commercially available, for example, from Shin-Etsu Chemical Co., Ltd. under the trade names

Methollose 60 SH-4000, Methollose 60 SH-10000, Methollose 90SH-4000, Methollose 90SH-15000, Methollose 90SH-30000 and Methollose 90SH-100000. These HPMC products have viscosities (2% aqueous solution, 20°C) of [, respectively,] 4000 cP, 10,000 cP, 4000 Cp, 15,000 cP, 30,000 Cp and 100,000 cP.

In general, the depot tablet contains at least one pharmaceutically active component (drug) and other additives necessary for drugs. Examples of pharmaceutically active components include theophyllin, aspirin, acetaminophen, ethenzamide, ibuprofen, naproxen, propranolol, methyldopa, furosemide, nifedipin, pindolol, captopril, erythromycin, procaninamid, quinonine gluconate, quinonine sulfate, isosorbide dinitrate, vitamin preparations like vitamins C, B_1, B_2, B_8 and folic acid, iron preparations like iron(II) sulfate and calcium chloride. These active components can, even if a hydrophilic active component or an effective component has to be used in high concentration, be efficiently incorporated into the base component. The amount of medical component that is to be added to the tablet varies in dependence on the characteristic properties of each particular active component that is selected, and amounts to 10 to 95 wt%.

Additives for drugs that are usually added to the tablet optionally in addition to said pharmaceutically-active components include, for example, vehicles, additives to facilitate pressing, stabilizers and surface-active agents. Specific examples of vehicles are corn starch, lactose, sucrose and mannose. A molding additive can be magnesium stearate, for example. These molding additives can be added to the tablet in an amount from 0.5 to 3.0 wt%.

In the case of a depot tablet of wet matrix type that is formed by the wet process, binders as other additives for drugs are added to them. In this case the said HPMC component, which is the depot base component, also acts as binder, but the tablet can just as easily contain other types of HPMC, hydroxypropylcellulose and/or polyvinylpyrrolidone. In general such a binder is used in an amount from 2 to 5 wt% with respect to the total weight of the tablet.

The depot tablet in accordance with the invention can be made by a dry or wet process. In the dry process the depot tablet is obtained by uniformly mixing a powdered pharmaceutically active component, an HPMC product as depot base component and a vehicle under dry conditions, and additionally a press-facilitating agent is added and the resulting mixture is pressed, for example with a rotary press machine. The said HPMC, which has sufficiently fine particle size and low bulk weight, is used as HPMC product. In the wet process on the other hand the depot tablet can be obtained by mixing a powdered pharmaceutically active component, an HPMC product with sufficient fine particle size and a vehicle in the presence of water, an organic solvent or mixture thereof in a high speed mixer, drying the resulting mixture and passing the dried product through a screen to obtain particles. The resulting particles are mixed with other additives such as a molding additive and molded under pressure in a rotary press machine.

When a depot tablet of this type is administered to a patient, the HPMC component contained in it swells in the patient's body because of rapid hydration and this way a gel layer forms on the surface of the tablet. The release rate of the pharmaceutically active component is highly affected by various factors like the molecular weight of the HPMC that forms the gel layer and its rate of hydration.

If HPMC particles with a size of not less than 0.15 mm mesh width (100 mesh) are molded under pressure, the particles produce dense agglomeration and this again prevents premature decomposition of the tablet in the initial stage of administration and any excessive administration of the drug contained in it. On the other hand, HPMC particles with a large particle size bring about agglomeration in molding under pressure, but the resulting additive will have high density. The apparent density highly affects the compression molding behavior of such particles, which agglomerate in a coarse fashion. If the bulk weight is less than 0.35 g/mL, the HPMC particles, which have a particle size of not less than 0.15 mm mesh width (100 mesh), produce an increase of hardness after compression molding and an increase of the hydration rate. On the other hand, if the bulk weight is low, the surface of the HPMC particles decreases and this brings about an improvement of the compression molding behavior of the particles.

The depot tablet in accordance with the invention with the said structure enables easy control of the release rate of a medical component up to a predetermined low level and enables continuous administration of the medical component in a predetermined concentration over a long period of time.

The invention is illustrated more precisely with reference to the following examples, but the invention is not in any way limited to these specific examples.

Example 1

After 200 mg salicylamide and 50 mg HPMC had been uniformly mixed together, the resulting mixture was molded at a pressure of 100 kg/cm^2 for 30 sec in an IR pressing machine, producing a depot tablet. The HPMC used here was HPMC 2910 (obtainable from Shin-Etsu Chemical Co., Ltd., under the trade name Methollose 60 SH-4000), of which at least 95 wt% could pass through a screen with 0.15 mm mesh size (100 mesh) and which had a bulk weight of 0.25 g/mL.

Example 2

The same process as in Example 1 was repeated except that the bulk weight of the HPMC that was used was adjusted to 0.30 g/mL.

Comparative Examples 1 and 2

The same procedure as in Example 1 was repeated except that the bulk weight of the HPMC that was used was adjusted to 0.45 g/mL or 0.55 g/mL.

Example 3

After uniformly mixing 240 mg theophyllin, 60 mg HPMC and 3 mg magnesium stearate in a twin cylinder mixer the resulting mixture was compression-molded in the usual way, producing a depot tablet. The HPMC used here was, as in Example 1, HPMC 2910, of which no less than 98 wt% could pass through a screen with 0.15 mm mesh size (100 mesh), and which had a bulk weight of 0.32 g/mL.

Comparative Example 3

The same process as in Example 3 was repeated except that an HPMC of which no less than 80 wt% could pass through a screen with 0.15 mm mesh size (100 mesh) and which had a bulk weight of 0.33 g/mL was used.

Example 4

After uniform mixing of 220 mg ethenzamide, 80 mg HPMC and 3 mg magnesium stearate in a twin cylinder mixer the resulting mixture was molded under pressure in the usual way, to produce a depot tablet. The HPMC used here was HPMC 2208 (obtainable from Shin-Etsu Co., Ltd, under the trade name Methollose 90 SH-100000), of which no less than 95 wt% could pass through a screen with 0.15 mm mesh size (100 mesh) and which had a bulk weight of 0.23 mm g/mL.

Quality Test

Each of the depot tablets that were produced in Examples 1 to 4 and Comparative Examples 1 to 3 was dissolved in a test solution according to the stirring procedure described in the Pharmacopoeia of Japan (Section 12); the release rate was determined in time intervals and the dissolving rate was then evaluated by means of the thus-determined release rate. The test solution used in this case was 900 mL water that was maintained at 37°C. The agitator speed was set to 100 rpm.

The resulting products are summarized in the following Table 1. In Table 1 the "elapsed time" in expressed hours and the "release rate" is expressed in wt%.

Table 1

Zeit (1)	Lösungsgeschwindigkeit (2)						
	Beispiele (3)				Vergleichsbeispiele (4)		
verstrichen (5)	1	2	3	4	1	2	3
0,5	13,2	17,4	6,2	2,5	21,5	26,2	49,6
1,0	17,1	21,9	11,3	4,1	26,6	32,4	56,7
2,0	23,2	27,9	19,7	7,6	32,6	39,7	65,8
4,0	34,3	44,7	32,6	14,1	44,5	55,1	80,3
6,0	44,0	49,6	48,7	19,8	55,1	64,1	91,1
8,0	54,9	59,0	60,9	25,1	63,0	71,5	98,8
12,0	71,9	75,0	80,0	35,6	78,0	88,2	--

Key: 1 Time
2 Dissolving rate
3 Examples
4 Comparative Examples
5 Elapsed

The products obtained in Examples 1 and 2 and in Comparative Examples 1 and 2 clearly show that the tablet began to decompose in the initial stage of administration, and the pharmaceutically active component was spontaneously released at a high rate, and the tablets did not show the desired long-term release characteristics when the bulk weight of the HPMC used exceeded 0.35 g/mL. The products obtained in Example 3 and in Comparative Example 3 show that the observed release rate corresponded to a release of zeroth order when HPMC particles of which no less than 95 wt% could pass through a screen with 0.15 mm mesh size (100 mesh) were used. On the other hand, it was found that the tablet begins to decompose in the initial stage of release and that the active component is released spontaneously at a high rate when using HPMC particles of which less than 95 wt% could pass through a screen with 0.15 mm mess size (100 mesh).

Claims

1. A depot tablet that contains as depot base component hydroxypropylmethylcellulose particles whose bulk weight is no more than 0.35 g/mL, where no less than 95 wt% can pass through a screen with 0.15 mm mesh size (100 mesh) and which have a degree of substitution of methoxy groups from 19 to 30 wt% and a degree of substitution of hydroxypropoxy groups from 4 to 12 wt%.

2. A depot tablet as in Claim 1, where the viscosity of a 2% aqueous solution of the hydroxypropylmethylcellulose is no less than 1000 cP, measured at 20°C.

3. A depot tablet as in Claim 1 or 2, where the content of hydroxypropylmethylcellulose in the tablet is 5 to 90 wt%.

Form P 1

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
APPLICATION FOR A PATENT AND ACKNOWLEDGEMENT OF RECEIPT
[Section 30 (1)—Regulation 22]

Revenue stamps or revenue franking machine impression Official date stamp

The grant of a patent is hereby requested by the undermentioned applicant on the basis of the present application filed in duplicate.

Official application No.		(i) Applicant's or agent's reference
21 01	95/7670	

(ii) 71 Full name(s) of applicant(s)

BOEHRINGER MANNHEIM GMBH

(iii) Address(es) of applicant(s)

SANDHOFER STRASSE 116
D-68298 MANNHEIM
FEDERAL REPUBLIC OF GERMANY

(iv) 54 Title of invention

PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND PROCESSES FOR THE PRODUCTION THEREOF

(v) X The applicant claims priority as set out on the accompanying form P 2. DE P 44 32 757.9 14.09.1994

(vi) This application is for a patent of addition to Patent Application No. 21 01

(vii) This application is a fresh application in terms of section 37 and based on Application No. 21 01

(v) This application is accompanied by:

X	1.	~~A single copy of a provisional or~~ two copies of a complete specification of 25 pages.
X	2.	Drawings of 1 sheets.
X	3.	Publication particulars and abstract (form P 8 in duplicate).
X	4.	A copy of Figure 1 of the drawings (if any) for the abstract.
X	5.	An assignment of invention.
X	6.	Certified priority document(s) (state number). DE p 44 32 757.9
X	7.	Translation of the priority document(s).
	8.	An assignment of priority rights.
	9.	A copy of the form P 2 and the specification of S.A. Patent Application No. 21 01
X	10.	A declaration and power of attorney on form P 3.
X	11.	Request for ante-dating on form P 4.
	12.	Request for classification on form P 9.
X	13.	FORM P2 PLUS COPY

(ix) 74 Address for service: HAHN & HAHN, PRETORIA

Dated this 13 day of SEPTEMBER 19 95

Received

Official date stamp

Dr. W.A. HAHN &
Dr. H.H. HAHN
PRETORIA

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
DECLARATION AND POWER OF ATTORNEY
(Section 30 – Regulations 8, 22(1)(c) and 33)

13.9.95

FORM P. 1

PATENT APPLICATION NO.	H & H REF:	LODGING DATE
21 01 957670		22 13.09.1995

FULL NAME(S) OF APPLICANT(S)

71 BOEHRINGER MANNHEIM GMBH

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EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
NOTE: The country must be indicated by its International Abbreviation – see schedule 4 of the Regulations.	33 DE	31 P 44 32 757.9	32 14.09.1994

TITLE OF INVENTION

54 PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND PROCESSES FOR THE PRODUCTION THEREOF

* I/We.

DR KOLB AND DR MINK

hereby declare that–

1. I/we am/are the applicant(s) mentioned above;

** 2. I/we have been authorised by the applicant(s) to make this declaration and have knowledge of the facts herein stated in the capacity of AUTHORISED OFFICERS of the applicant(s);

*** 3. the inventor(s) of the abovementioned invention is/are the person(s) named above and the applicant(s) has/have acquired the right to apply by virtue of *an assignment from the inventor(s)*;

4. to the best of my/our knowledge and belief, if a patent is granted on the application, there will be no lawful ground for the revocation of the patent;

**** 5. this is a convention application and the earliest application from which priority is claimed as set out above is the first application in a convention country in respect of the invention claimed in any of the claims; and

6. the partners and qualified staff of the firm of **Dr. W.A. HAHN & Dr. H.H. HAHN**, patent agents, are authorised, jointly and severally, with powers of substitution and revocation, to represent the applicant(s) in this application and to be the address for service of the applicant(s) while the application is pending and after a patent has been granted on the application.

SIGNED AT Mannheim THIS 17th DAY OF August, 19 95

FIRST RECEIVED IN RSA ON: 31-8-95
WEBBER WENTZEL PATENT AGENTS

BOEHRINGER MANNHEIM GMBH
ppa. i.V.
Dr. Kolb procurist
Dr. Mink signed for
SIGNATURE(S)
(no legalization necessary)

*In the case of applications in the name of a Company, Partnership or Firm, give full names of signatory/signatories, delete paragraph 1, and enter capacity of each signatory in paragraph 2.

**If the applicant is a natural person, delete paragraph 2.

***If the right to apply is not by virtue of an assignment from the inventor(s), delete 'an assignment from the inventor(s)' and give details of acquisition of right.

****For non-convention applications delete paragraph 5.

HAHN & HAHN (incorporated within WEBBER WENTZEL)

FORM P.7
(To be lodged in duplicate)

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

COMPLETE SPECIFICATION

(Section 30(1) - Regulation 28)

Official Application No		
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Full name(s) of applicant(s)

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Full name(s) of inventor(s)

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Title of invention

54 PHARMACEUTICAL PREPARATION CONTAINING METFORMIN AND PROCESSES FOR THE PRODUCTION THEREOF

South African Application

Boehringer Mannheim GmbH
4061/00/

Pharmaceutical preparation containing metformin and processes for the production thereof

The invention concerns pharmaceutical preparations containing metformin hydrochloride (also named metformin in the following) as the active substance and a hydrocolloid former as a retarding agent and a process for the production thereof.

It is known that metformin hydrochloride is a biguanide derivative (1,1-dimethyl-biguanidemonohydrochloride) that has an oral antidiabetic action. Metformin sustained-release tablets containing 850 mg metformin hydrochloride per film tablet (Glucophage® retard) are available on the market. Since in contrast to other active substances, metformin cannot be pressed as a pure substance (the material disintegrates after compression and is unchanged), structure-forming auxiliary substances such a polyvinyl acetate have been utilized as retarding agents for these high-dose sustained-release tablets (Lipha, "Fachinformation" Glucophage , August 1991; "Bundesverband der Pharmazeutischen Industrie e.V." Editor, "Rote Liste" 1993, Edition Cantor, Aulendorf 1993). The mechanism of action of such structural tablets is based on the fact that the readily water-soluble metformin diffuses out of the tablet in the gastro-intestinal tract independent of pH while the tablet structure with its coating is eliminated again almost unchanged.

The disadvantage of using such structure-forming auxiliary substances such as polyvinyl acetate is, however, that they have to be processed with organic solvents especially in the granulation process and the organic solvent has to be removed again as completely as possible before the granulate can be processed further into compressed pharmaceutical forms of administration and for example pressed into tablets.

A need exists to provide a pharmaceutical composition in the form of a readily-compressible granulate which contains the active substance metformin with the highest possible content of active substance and a retarding agent which leads to a controlled release of the active substance in which the pharmaceutical composition, however, contains no structure-forming builders which have to be processed with organic solvents but whose composition should be based on substances that can be processed aqueously. It should be possible to easily compress these pharmaceutical compositions so that they are suitable for the production of solid pharmaceutical forms of administration such as e.g. tablets, dragées or compacts for filling capsules. In the production of tablets or other compacts the total weight should be no more than about 1200 - 1300 mg in order not to jeopardise therapeutic safety (patient compliance) since patients often do not take larger oral forms of administration as regularly as prescribed.

A further need exists to solve the problem of capping that is caused by the active substance and is particularly pronounced in the case of metformin during the processing of the granulate for these high-dose forms of administration in particular during the

production of tablets in order to avoid losses of yield during production and impairment of pharmaceutical quality. Capping denotes the detachment of pressed material in layers from the manufactured compact during pressing or shortly thereafter (Schepky G. in: Bruchhausen F. von et al.; editors: "Hagers Handbuch der pharmazeutischen Praxis, vol. 2, methods, 5th edition, Springer Verlag, Berlin 1991). In the case of metformin, particularly when the content of active substance in the granulate is highly dosed, it has turned out that the tendency of capping is particularly high during the production of tablets.

The causes for these tabletting problems may be manifold and complex. Capping can be triggered by an inadequate binder action, the moisture content of the granulate being too high or too low, unsuitable crystal forms, strongly aerophilic substances, porosity which is too high, a powder content which is too high, inter-particulate binding between the granulate particles which is too strong and by unsuitable granulate forms. Machine-dependent factors that can lead to capping may be excessive pressing forces, badly used or worn tools, too excessive pressing rates and poor deaeration of the mould (static pressure). In the case of the active substance metformin it has, however, turned out that the usual methods are not adequate to satisfactorily deal with capping of the tablet mass. A relatively high proportion of defective tablets have been regularly found in the production of the tablets and the tabletting had to be discontinued due to the high reject rates.

The invention provides

pharmaceutical compositions

containing high doses of metformin which contain a hydrocolloid former as a retarding agent and which has 0,5 - 3 % by weight residual moisture in the pharmaceutical composition. These pharmaceutical compositions can be produced advantageously using aqueous solvents so that organic solvents are no longer required. In addition these compositions can surprisingly be readily compressed. They are therefore particularly suitable for the production of solid pharmaceutical forms of administration such as e.g. tablets, dragées or capsules and these can be manufactured with the aid of conventional processing machines on a technical scale and in good quality as well as in high yield without incurring large losses due to undesired capping. The invention therefore also concerns a corresponding process for the production of these solid forms of administration in which the appropriate pharmaceutical compositions according to the invention are used in the form of granulates with 0,5 - 3 % by weight residual moisture. The residual moisture is preferably 1 - 2,5 % by weight, in particular 1,5 - 2 % by weight.

Surprisingly it was also found that in the case of the granulate according to the invention the addition of humectants which is otherwise often required to set a constant residual moisture until the granulate is compressed, can be omitted. This is particularly advantageous since this minimizes the addition of auxiliary substances and pharmaceutical compositions with a relatively high content of active substance are obtained. In addition these compositions have the advantage that they are stable on storage with respect to moisture content over a period of two or more days (calculated from manufacture until the granulate is used

for tabletting) before being compressed without the occurrence of any discernible disadvantageous changes in the composition. This is a particular advantage since this allows several partial lots of production batches of the pharmaceutical composition to be produced which can then be mixed as a compressible mass at a later time point in a common last process step and it can be processed into solid pharmaceutical forms of administration. In addition it surprisingly turned out that the use of a hydrocolloid former enabled in particular the poor compressibility known for metformin to be brought under control for the first time in a technically satisfactory manner. The solution according to the invention also ensured the desired retardation and compressibility by selection of a hydrocolloid former as a retarder and by appropriate control of the production process (adhering to the critical residual moisture of 0,5 - 3 % by weight) although the proportion of the hydrocolloid former in the formulation is exceptionally low. This is even more surprising since the active substance comprises the major portion of the formulation (about 70 - 95 % by weight), the water-sorption capacity of which is very low (the pure active substance only binds 0,04 % by weight water at a relative humidity of 90 %).

The percentage by weight of the active substance in the high-dose pharmaceutical composition is in the range of at least 70 % by weight, preferably 80 - 95 % by weight relative to the pharmaceutical composition. The active substance can be used in the form of acid addition salts of inorganic or organic acids such as e.g. hydrochloric acid, formic acid, acetic acid, maleic acid, tartaric acid or fumaric acid. The hydrochloride salt is preferably used.

The proportion of hydrocolloid former in the pharmaceutical composition is up to 15 % by weight, preferably 4 - 10 % by weight in particular about 6 - 8 % by weight.

The common hydrophilic gel formers are suitable as hydrocolloid formers or as hydrophilic swelling agents within the sense of the invention such as for example cellulose derivatives, dextrins, starches, polymers based on carbohydrate, natural and hydrophilic gums, xanthans, alginates, gelatins, polyacrylic acid, polyvinyl alcohol or polyvinyl pyrrolidone. In the case of cellulose derivatives alkyl or hydroxyalkylcellulose derivatives preferably come into consideration such as e.g. methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose or sodium carboxymethylcellulose. In a preferred working variant of the invention, methylhydroxypropylcellulose (MHPC) is used. The hydrocolloid formers can be used individually as well as in mixtures of two or several colloid formers. The common polymers used for pharmaceutical purposes with different degrees of substitution and/or different molecular weights corresponding to different degrees of viscosity of the aqueous solution can be used as suitable polymeric colloid formers based on cellulose.

The use of hydrocolloid formers as retarding agents is based on the property of hydrocolloid formers of being able to form a gel matrix on contact with release medium or digestive juices which erodes and releases the active substance. The combined effect of the amount of hydrocolloid former and degree of viscosity determines the time course of release in this case. Thus for

example riboflavin can be retarded for several hours by using a high proportion (70 - 95 % in relation to the core weight of a tablet) of polyvinyl alcohol of a low or medium viscosity level (Möckel J.E., Lippold B.C., Pharm. Research, 1993, 10, 1066-1070).

The compressed forms of administration that are manufactured using the pharmaceutical composition according to the invention such as for example sustained-released metformin tablet cores can be additionally provided with a film coating. The film coating can on the one hand cause an additional retardation by using those film materials which represent film formers that are usually suitable for this purpose. On the other hand the film coating may be a taste-neutralizing film former to which dyes can be added if desired. In addition it is also possible to use films resistant to gastric juice. The percentage by weight of the film coating relative to the final tablet is in the usual range of 0,3 - 3,0 % by weight, preferably of 0,8 - 1,2 % by weight. Film formers which come into consideration are common film formers such as for example ethylcellulose, poly(methylmethacrylate) derivatives (Eudragit®) and also soluble cellulose derivatives such as methylhydroxypropylcellulose and cellulose derivative for forming films resistant to gastric juice such as cellulose acetate-phthalate or methyl-hydroxypropylcellulose. Ethylcellulose is preferably used. The film formed can delay the dissolution of the active substance. The film coating may contain emollients, pore formers and pigments as the common auxiliary substances.

The pharmaceutical forms of administration according to the invention such as e.g. tablets contain - in addition

to the active substance whose percentage in the form of administration is in the range of 70 - 95 % by weight (for example 850 mg of the active substance is preferably used in the case of sustained-release tablets) and the retarding agent - preferably 2 - 10 % by weight binding agent, up to 2 % by weight, preferably 0,1 - 0,3 % by weight flow regulation agent and up to 2 % by weight preferably 0,4 - 1,1 % by weight lubricant in each case relative to the total weight of the mass ready for tabletting or to the tablet core. The usual agents such as for example colloidal silicon dioxide come into consideration as flow regulation agents for the tablet according to the invention. Talcum or stearic acid or alkali or alkaline-earth salts thereof, in particular magnesium stearate, are for example suitable as lubricants. Cellulose derivatives especially alkylcellulose and hydroxyalkylcellulose and in particular methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxycellulose, dextrins, starches, special soluble starches, other polymers based on carbohydrates such as e.g. galactomannans, natural gums such as gum arabicum, traganth, sterculia, acacia and others, xanthans, alginates, polyacrylic acid, polyvinyl alcohol and polyvinyl pyrrolidone can be used for example as binding agents. Polyvinyl pyrrolidone is preferred.

The pharmaceutical forms of administration according to the invention such as e.g. tablets are manufactured by mixing together the active substance, the retarding agent or a portion of the retarding agent and if desired, further auxiliary substances in the dry state, wet-granulating with water or an aqueous solution of a binding agent, drying the mass ready for tabletting to a

desired residual moisture and afterwards if necessary mixing the other portion of the retarding agent or other pharmaceutical substances with the granulate so that a residual moisture of 0,5 - 3 % by weight is obtained in the pharmaceutical composition in the last step of the process. In the wet-granulation a portion of the active substance, the auxiliary substances used and the retarding agent can be present totally or partially dissolved or suspended in water. If necessary organic solvents miscible with water can also be added such as for example acetone or lower alcohols such as methanol or ethanol.

The setting of the residual moisture is preferably achieved while drying in a fluidized bed process in which the wet-granulate is dried until the measured humidity in the exhaust air reaches the value determined in dried material in the course of a calibration for residual moisture. The composition produced in this manner is subsequently processed in the usual manner into pharmaceutical forms of administration and for example pressed into tablets. The tablets can be coated with a film using the usual coating processes. It is found that the residual moisture of 0,5 - 3 % by weight set with the aid of the hydrocolloid former ensures that the mass ready for tabletting can be compressed over the entire range of pressing power necessary to manufacture large tablets.

The active substance can be completely or partially processed into a granulate with the hydrocolloid former used for retardation or the hydrocolloid former is completely admixed with a hydrocolloid former-free granulate after its manufacture. However, an additional improvement in tabletting properties is achieved when

the hydrocolloid former or a part thereof is granulated with the active substance.

The coating of the tablet is carried out according to conventional methods such as e.g. the coating pan and or fluidized bed process.

The sustained-release tablets according to the invention release metformin in a controlled manner over a period of 0,5 - 10 hours preferably over 4 hours (Fig. 1). The weight of the tablets is 1200 mg at most and preferably below 1000 mg due to the fact that large amounts of additional auxiliary substances and especially humectants such as e.g. glycerol or sorbitol are not necessary due to the use of the hydrocolloid former.

It is intended to elucidate the invention by practical examples without limiting it thereto.

In the following examples 1 - 6 the residual moisture was set in a range of 1,95 - 2,80 % by weight before the pharmaceutical composition was pressed into tablets in the form of a compressible mass.

Example 1:

Hydrocolloid former: methylhydroxypropylcellulose. The proportion of MHPC can be varied e.g. from 40 - 95 mg.
Residual moisture: 2,1 %

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
Core:		
metformin hydrochloride	850,00	850,00
methylhydroxypropylcellulose	60,00	60,00
polyvidone	38,00	38,00
magnesium stearate	5,00	5,00
core total:	953,00	953,00
film coating:		
methylhydroxypropylcellulose	20,00	20,00
ethylcellulose	12,00	12,00
Macrogol	4,00	4,00
titanium dioxide	4,00	4,00
coating total:	40,00	40,00
film tablet total:	993,00	993,00

Production:
The granulate for an amount of about 1 million tablets is produced in five partial batches. 170 kg metformin hydrochloride and 12 kg methylhydroxypropylcellulose are dry mixed with one another for each of the five partial batches

and wet-granulated in a mixer with a 10 % aqueous binding agent solution of polyvidone. Afterwards the granulate is dried in a fluidized bed granulator until it has an adequate residual moisture. The five partial batches are combined and mixed with 5 kg magnesium stearate. The compressible mass is tabletted. The tablet cores are coated in a coating pan using the composition described for the film.

The above-mentioned formulation is adjusted to a residual moisture of 2,1 %. The tabletting proceeds without difficulty i.e. no capping of the manufactured tablet mass is found.

Example 2:

Hydrocolloid former: hydroxyethylcellulose
residual moisture: 2,0 %

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
core:		
metformin hydrochloride	850,00	850,00
hydroxyethylcellulose	70,00	70,00
polyvidone	40,00	40,00
magnesium stearate	5,00	5,00
core total:	965,00	965,00
film coating:		
methylhydroxypropylcellulose	5,00	5,00
lactose	5,00	5,00
ethylcellulose	10,00	10,00
Macrogol	3,00	3,00
titanium dioxide	3,00	3,00
coating total:	26,00	26,00
film tablet total:	991,00	991,00

The granulate is produced and processed further analogous to example 1; the tabletting proceeds without problems.

Example 3:

Hydrocolloid former: sodium carboxyethylcellulose
residual moisture: 2,1 %

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
core:		
metformin hydrochloride	850,00	850,00
sodium carboxyethylcellulose	80,00	80,00
polyvidone	35,00	35,00
magnesium stearate	5,00	5,00
core total:	970,00	970,00
film coating:		
methylhydroxypropylcellulose	5,00	5,00
ethylcellulose	10,00	10,00
Macrogol	4,00	4,00
titanium dioxide	3,00	3,00
coating total:	22,00	22,00
film tablet total:	992,00	992,00

The granulate is produced and processed further analogous to example 1; the tabletting proceeds without problems.

Example 4:

Hydrocolloid former: polyacrylic acid
residual moisture: 2,8 %

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
core:		
metformin hydrochloride	850,00	850,00
polyacrylic acid	60,00	60,00
methylhydroxypropylcellulose	30,00	30,00
magnesium stearate	5,00	5,00
core total:	945,00	945,00
film coating:		
methylhydroxypropylcellulose	10,00	10,00
ethylcellulose	10,00	10,00
Macrogol	3,00	3,00
titanium dioxide	3,00	3,00
coating total:	26,00	26,00
film tablet total:	971,00	971,00

The granulate is produced and processed further analogous to example 1. However, methylhydroxypropylcellulose is used in this case as a binding agent. The tabletting proceeds without problems.

Example 5:

Hydrocolloid former: hydroxypropylcellulose
residual moisture: 1,95 %

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
core:		
metformin hydrochloride	850,00	850,00
hydroxypropylcellulose	60,00	60,00
polyvidone	40,00	40,00
magnesium stearate	5,00	5,00
core total:	955,00	955,00
film coating:		
poly(ethylacrylate-methyl methacrylate) dispersion 30 %	6,00*	6,00*
talcum	1,20	1,20
antifoaming agent	0,07	0,07
coating total:	7,27	7,27
film tablet total:	962,270	962,270

*The stated weight relates to the dry substance.

The granulate is produced and processed further analogous to example 1. However, the hydrocolloid former hydroxypropylcellulose in this case is not granulated concurrently but rather dry mixed with the final granulate.

Example 6:

Hydrocolloid former: methylhydroxypropylcellulose
residual moisture: 2,0 %

In the following example an additional binding agent is completely omitted, the methylhydroxypropylcellulose used simultaneously functions as a binding and retarding agent.

Components:	Tablet [mg]	compressible mass [kg/1 mio pieces]
core:		
metformin hydrochloride	850,00	850,00
methylhydroxypropylcellulose	100,00	100,00
magnesium stearate	5,00	5,00
core total:	955,00	955,00
film coating:		
methylhydroxypropylcellulose	20,00	20,00
ethylcellulose	12,00	12,00
Macrogol	4,00	4,00
titanium dioxide	4,00	4,00
coating total:	40,00	40,00
film tablet total:	995,00	995,00

Production:
The granulate is produced in 5 partial batches. 170 kg of the active substance metformin hydrochloride and 18 kg methylhydroxypropylcellulose are admixed in a fluidized bed granulator. 2 kg methylhydroxypropylcellulose is dissolved in 50 l water. The dry mixture is granulated with the binding agent solution in a fluidized bed granulator and subsequently

dried. The five partial batches are combined and mixed with 5 kg magnesium stearate. This compressible mass is tabletted. The tablet cores are coated in a coating pan with the film having the described composition.

Example 7:

Hydrocolloid former: methylhydroxypropylcellulose
residual moisture: 0,49 %

In the formulation stated below a moisture of 0.49 % was obtained. Due to the high loss caused by capping, the tabletting had to be discontinued.

Components:	Tablet [mg]
core:	
metformin hydrochloride	850,00
methylhydroxypropylcellulose	40,00
polyvidone	38,00
magnesium stearate	5,00
core total:	953,00
film coating:	
methylhydroxypropylcellulose	20,00
ethylcellulose	12,00
Macrogol	4,00
titanium dioxide	4,00
coating total:	40,00
film tablet total:	993,00

Example 8:

Hydrocolloid former: gelatin
residual moisture: 0,48 %

In the formulation stated below a moisture of 0,48 % was obtained. Due to the high loss caused by capping, the tabletting had to be discontinued.

Components:	[mg]
core:	
metformin hydrochloride	850,00
lactose	70,00
gelatin	40,00
silicon dioxide, highly dispersed	2,00
magnesium stearate	2,50
core total:	964,50
film coating:	
methylhydroxypropylcellulose	10,00
ethylcellulose	9,00
diethyl phthalate	3,00
titanium dioxide	3,00
coating total:	25,00
film tablet total:	989,5

Claims

1. **Pharmaceutical composition containing metformin as the active substance and a hydrocolloid former as a retarding agent** wherein the residual moisture in the pharmaceutical composition is 0,5 to 3% per weight.

2. Pharmaceutical composition as claimed in claim 1 including conventional pharmaceutical auxiliary substances.

3. **Pharmaceutical composition** as claimed in either one of claims 1 & 2, **wherein the content of the active substance metformin is at least 70 %.**

4. **Pharmaceutical composition** as claimed in any one of claims 1 to 3, **wherein the amount of hydrocolloid former is 4 - 15 % by weight.**

5. **Pharmaceutical composition as claimed in one of the claims 1 - 4, wherein the hydrocolloid former is selected from the group comprising cellulose derivatives, dextrins, starches, polymers based on carbohydrates, natural gums, xanthans, alginates, gelatins, polyacrylic acid, polyvinyl alcohol and polyvinylpyrrolidone.**

6. **Pharmaceutical composition as claimed in claim 5, wherein the hydrocolloid former is a cellulose derivative in particular an alkyl or hydroxyalkyl-cellulose.**

7. Pharmaceutical composition as claimed in claim 6, wherein the hydrocolloid former is selected from methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxpropylcellulose, methylhydroxyethylcellulose, methylhydroxypropyl-cellulose or sodium carboxymethylcellulose.

8. Pharmaceutical composition as claimed in one of the claims 1 - 7 containing 3 - 5 % by weight binding agent, up to 2 % by weight flow regulation agent and up to 2 % by weight lubricant.

9. Pharmaceutical composition as claimed in one of the claims 1 - 7 for the production of compressed solid pharmaceutical forms of administration in particular of tablets or compacts for filling into capsules.

10. Pharmaceutical form of administration in the form of tablets or compacts for filling into capsules containing metformin as the active substance and a hydrocolloid former as a retarding agent with a residual moisture of 0,5 - 3 % by weight relative to the weight of the tablet core or the fillmass of the capsule.

11. Pharmaceutical form of administration as claimed in claim 10 in the form of a tablet having a final weight below 1300 mg.

12. Process for the production of pharmaceutical compositions containing metformin as the active substance and a hydrocolloid former as a retarding agent, wherein the active substance and the retarding agent or a portion thereof are granulated with an aqueous solvent containing binding agents if necessary.

13. A process as claimed in claim 12, wherein the pharmaceutical compositions contain additional common auxiliary substances.

14. A process as claimed in claim 13, wherein the other portion of the retarding agent or other common auxiliary substances are admixed with the granulate.

15. A process as claimed in any one claims 12 to 14, wherein the granulate is compressed into tables.

16. A process as claimed in claim 15, wherein the tables are subsequently coated with a film coating if desired.

17. A process as claimed in any one claims 12 to 14, wherein the granulate is compacted and filled into capsules.

18. A process as claimed in any one of claims 12 to 14, wherein methylhydroxypropylcellulose is used as the hydrocolloid former.

19. A process as claimed in any one of claims 12 to 14, wherein up to 2% by weight flow regulation agent, up to 2% by weight lubricant and up to 5% by weight binding agent relative to the complete pharmaceutical composition are used for the production of the granulate.

20. Use of pharmaceutical compositions as claimed in one of the claims 1 to 9 for the production of compressed pharmaceutical forms of administration in particular of tables or compacts for filling capsules.

21. A pharmaceutical composition for the treatment of diabetes including metformin as active substance and a hydrocolloid former as a retarding agent wherein the residual moisture in the pharmaceutical composition is 0,5 to 3% by weight.

22. A pharmaceutical composition as claimed in any one of claims 1 to 9 and 21, substantially as hereinbefore described or exemplified.

23. A pharmaceutical form of administration as claimed in either one of claims 10 and 11, substantially as hereinbefore described or exemplified.

24. A process according to the invention for production of pharmaceutical compositions, substantially as hereinbefore described or exemplified.

25. Use as claimed in claim 20, substantially as hereinbefore described or exemplified.

26. A pharmaceutical composition or pharmaceutical form of administration as claimed in any one of claims 1 to 11 and 21 to 23 whenever supplied with instructions for the use thereof in the treatment of diabetes.

27. A pharmaceutical composition or pharmaceutical form of administration as claimed in claim 26 when the instructions are in printed or written form.

28. A pharmaceutical composition or pharmaceutical form of administration as claimed in claim 27 supplied in a package or container having the said instructions provided therein or thereon.

DATED THIS 13 DAY OF SEPTEMBER 1995.

N. M. v. NIEKERK

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